Mammographic Densities and Risk of Breast Cancer

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To determine the relation of mammographic densities to subsequent breast cancer risk, a case–control study was undertaken using prediagnostic mammograms of screening program participants. Mammograms of cases (n = 266) and controls (n = 301) were blindly assessed for mammographic densities, which were measured by planimetry. The odds of breast cancer increased steadily with increasing breast density (test for trend, $P < 0.0001$). Breast cancer odds was 1.7 for densities between 5% and 24.9%, 2.5 for 25% through 44.9%, 3.8 for 45% through 64%, and 4.3 for densities of 65% and greater (referent = <5% densities). Odds ratios also increased with increasing densities among women with the P2 and DY mammographic patterns. These findings suggest that the percentage of mammographic densities in the breast can predict breast cancer risk more accurately than a qualitative assessment of mammographic patterns. *Cancer* 67:2833–2838, 1991.

On MAMMOGRAPHY, normal cancer-free breast tissue represents a continuum of breast types ranging from fatty breasts with no measurable mammographic densities to those displaying extensive regions of density. Mammographic densities are areas of breast tissue seen radiographically over and above that of fat. The densities are composed of epithelial and connective tissue, the type of tissue from which most breast neoplasms develop.

To determine whether the extent of mammographic densities is associated with risk of breast cancer, Wolfe *et al.*[1] developed a method to measure areas of mammographic density that employs a planimeter. This method was first applied in a small case–control study of breast cancer that utilized mammograms taken within 8 weeks bef re surgery.[1] Results from this study suggested that percent mammographic densities was a significant risk factor for breast cancer, although a dose–response relationship was not observed.

In the current study, we had the opportunity to assess mammograms taken 4 years before the diagnosis of breast cancer among screening program participants to determine if the percentage of mammographic densities is predictive of breast cancer risk using prediagnostic mammograms. This study design enabled us to conduct blinded assessments of densities within the breast in which a tumor subsequently developed.

Methods

The study population consisted of women enrolled at 25 of the 29 screening centers (four centers declined to provide mammograms) of the Breast Cancer Detection and Demonstration Projects (BCDDP), a nationwide screening program sponsored by the National Cancer Institute and the American Cancer Society. This multicenter screening program provided annual breast examinations.

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mammography, and thermography to more than 280,000 volunteer women for 5 years, from 1973 through 1975.

The 266 case subjects were enrolled during the first year of the project and were newly diagnosed with unilateral breast cancer during the fifth year (1978 through 1980). None of breast cancer subjects had a prior history of the disease. Women with bilateral breast cancer (n = 6) were deleted from the analysis. The 301 control subjects did not have breast cancer during the 5-year screening period and were matched to case subjects on screening center, 5-year age group, race (white, black, Asian, and other), date of entry into the project (within 6 months), and duration of screening participation.

Data on breast cancer risk factors were collected through in-home interviews lasting 1 hour. The interviews were conducted as part of a large case–control study, described in detail elsewhere.[2] The questionnaire focused on medical and reproductive history, family history of breast cancer, body build, hormone use, drinking and smoking habits, and demographic characteristics. Interviews were completed for 85.4% of the case subjects eligible for the current study and 90.4% of their matched controls.

To assess the percentage of mammographic densities, the radiologist (J. N. W.) read prediagnostic mammograms taken during the first screening year (*i.e.*, 4 years before the case subjects were diagnosed with breast cancer). Among the breast cancer cases, we analyzed densities for the breast in which the tumor developed. The breast corresponding to the same side was analyzed for each matched control subject. To prevent measurement bias, the radiologist was blinded to patient age, examination date, screening center, and breast cancer status.

Mammographic parenchymal patterns were also assessed to determine if breast cancer risk increased with increasing percent densities among women in the P2 or DY categories. Wolfe's classification of mammographic parenchymal patterns consists of four breast patterns: N1, P1, P2, and DY.[3] The N1 breast is fatty with no measurable mammographic densities. The P1 breast has up to 25% nodular densities, which appear as bead-like structures on mammography. The P2 breast has over 25% nodular mammographic densities. The DY breast typically contains extensive regions of homogenous mammographic densities, which appear as sheet-like regions. No ductal densities are visible in the DY breast.[3]

The radiologist (J. N. W.) outlined all areas of mammographic densities on the craniocaudal view using a china marker. Isolated calcifications, biopsy scars, Cooper's ligaments, and breast masses were not considered in this assessment. The total area of the breast and the outlined regions of mammographic densities were measured by one of the authors (M. S.) using a compensating polar planimeter (LASICO, Los Angeles, CA). The percentage of radiographic densities was calculated by dividing the area with densities by the total breast area.

A multivariate analysis of variance[4] was conducted among the control women to identify breast cancer risk factors independently associated with mammographic densities. Variables evaluated in this analysis included age, weight, height, and menopausal status at entry to the screening program, first-degree family history of breast cancer, number of live births, age at first live birth, years of education, age at menarche, oral contraceptive and replacement estrogen use, age at and type of menopause, and number of breast biopsies before entering the screening program. Using the percentage of mammographic densities as the dependent variable, we fit a model that retained the variables most highly correlated with this measure ($P < 0.10$).

Odds ratios were calculated to determine the association between breast cancer risk and five categories of percentage mammographic densities: less than 5%, 5% through 24.9%, 25% through 44.9%, 45% through 64.9%, and 65% and greater. Women who had mammographic densities of less than 5% served as the referent group for all case–control comparisons. When analyzing population subgroups, we combined the two highest categories of percentage densities to compensate for small numbers of women in these strata.

Unconditional logistic regression analysis was used to obtain adjusted odds ratios and to investigate the potential effects of interaction and confounding.[5-7] Although the study design was matched, unmatched analyses resulted in similar, but more stable, estimates of relative risk by retaining more case–control pairs than the matched analyses.[8] Risk factors evaluated for first-order interactions were age, menopausal status, first-degree family history of breast cancer, body weight, height, and parity. The log-likelihood ratio test was used to determine statistical significance of interactions on a multiplicative scale.[6,7] Risk factors evaluated for confounding were selected *a priori* on the basis of their association with breast cancer risk. The final logistic model was determined by removing variables one at a time from the full model. We retained a variable if its presence in the model was judged to influence the odds ratios associated with the five categories of mammographic density. Age at entry was retained in the model because it was a matching factor. The test for linear trend in odds ratios associated with percentage densities was performed by scoring this categorical variable with an ordered code (*i.e.*, 1, 2, 3, 4) and treating it as a continuous variable.

To evaluate intraobserver reliability, a 10% sample of the study mammograms was selected and reread. The reliability mammograms were mixed with the radiologist's regular batches of study mammograms to prevent knowledge of which images were repeat readings. Data from the first and second readings were cross-tabulated and agreement was calculated for the five categories of mammographic densities.[9] Agreement was also analyzed according to image quality, as judged by the radiologist at the time of the assessment.

Results

Case and control subjects were similar by age, race, marital status, and educational attainment. The median age at the time of entry into the project was 54 and 53 years of age among cases and controls, respectively. Ninety percent of the study population was white, 6% black, and 4% of Asian or other minority races. Most women had ever been married (95%). In addition, the study subjects were well educated: most women had graduated from high school (89%) and nearly 50% had attended college.

Case subjects had higher percentages of mammographic densities than control women (Fig. 1). Twelve percent of case subjects and 23% of controls had mammographic densities of less than 5%. Forty-five percent of case subjects and 32% of controls had mammographic densities of 45% or greater. The mean percentages of mammographic density were 38% for case subjects and 31% for controls.

A multivariate analysis of variance among the control subjects showed that the percentage of mammographic densities decreased with increasing patient age, body weight, and number of live births (Table 1). Height was directly associated with percent densities; however, this association was not as strong or consistent as the association of densities with weight and age.

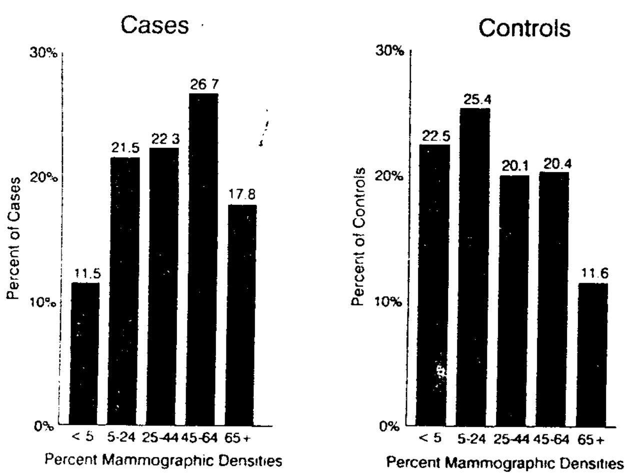

FIG. 1. Distribution of cases and controls by percentage of breast area with radiographic densities. Breast Cancer Detection and Demonstration Project.

TABLE 1. Adjusted Mean Percent of Breast Area Containing Mammographic Densities Among Controls by Characteristics Associated With Percent Mammographic Density, Breast Cancer Detection and Demonstration Project*

Risk factor	No. of controls	Mean % density†
Age at entry (yr)		
35–44	56	45.9
45–49	46	31.4
50–54	52	27.6
55–59	53	25.7
60–74	72	23.1
Weight at entry (kg)		
<55	65	46.0
55–60	74	32.5
61–69	64	28.3
70+	76	16.6
No. of live births		
0	40	35.7
1	38	33.9
2	73	30.3
3	67	28.5
4+	61	26.8
Height (cm)		
<157.5	46	24.3
157.5–162.5	74	30.7
162.6–167.5	94	32.2
167.6+	65	31.6

* Unknowns excluded from analysis.

† Adjusted for age at entry, weight at entry, no. of live births, and height.

Table 2 shows the crude and adjusted odds ratios estimated from the final logistic model. The risk of having breast cancer increased steadily with increasing percent densities, with the highest odds of breast cancer associated with densities of 65% or greater (OR = 4.3; 95% confidence interval [CI], 2.1 to 8.8). The test for linear trend in the odds ratios was statistically significant ($P < 0.0001$). In addition, the odds of breast cancer associated with 45% or greater mammographic densities was comparable with or greater than that associated with traditional risk factors for breast cancer in this study population.

TABLE 2. Adjusted Breast Cancer Odds Ratios Associated With Percentage of Breast Area Containing Mammographic Densities, Breast Cancer Detection and Demonstration Project*

% densities	Cases (no.)	Controls (no.)	Crude odds ratio†	Adjusted odds ratio‡	95% confidence interval
<5	29	64	1.0	1.0	Referent
5–24.9	54	72	1.7	1.7	(1.0–3.1)
25–44.9	56	57	2.2	2.5	(1.4–4.6)
45–64.9	67	58	2.8	3.8	(2.0–7.1)
65+	45	33	3.5	4.3	(2.1–8.8)

* Unknowns excluded from analysis.

† Adjusted for age at entry (continuous variable).

‡ Simultaneously adjusted for age at entry (continuous variable), weight at entry (<55, 55–59, 60–64, 55–74, and 75+ kg), and no. of live births (0, 1, 2, 3, 4+).

To test for interaction, densities were analyzed as a risk factor in several population subgroups. The odds of breast cancer associated with percentage densities was similar among women of different ages (less than 50, greater than or equal to 50 years of age), menopausal status at entry, weight at entry (less than 63.5 kg, greater than or equal to 63.5 kg), height (less than 167.6 cm, greater than or equal to 167.6 cm), and parity (nulliparous, parous). Stratification by first-degree family history of breast cancer showed no major differences between the two groups for odds ratios among women with densities of more than 5% (referent = women with no family history and less than 5% densities). However, among women with less than 5% mammographic densities, a positive family history exerted only a small influence on the risk of breast cancer (OR = 1.4; 95% CI, 0.4 to 5.0). Statistical tests for the interaction of family history of breast cancer and mammographic densities under the additive and multiplicative models were not statistically significant.

To determine if there was heterogeneity in the risk of breast cancer within parenchymal pattern categories, we evaluated the odds of breast cancer associated with densities among women with the P2 and DY patterns. Odds ratios increased with increasing percentage densities among women with P2 and DY patterns (Table 3). P2 women with less than 45% densities had an odds ratio of 2.4, whereas P2 women with 65% or greater densities had 3.5-fold higher risks of breast cancer. DY women with less than 45% densities were not at increased risk of breast cancer. In contrast, DY women with 45% or greater densities had a 4.7-fold increased risk of breast cancer.

Cross-tabulation of the first and second readings of the reliability sample mammograms (n = 275) indicated that agreement on the five categories of percent mammographic densities was 77%. As expected, agreement increased with improving image quality with 85% agreement on mammograms of excellent quality, 76% on mammograms of good quality, and 69% on mammograms of fair or poor quality.

TABLE 3. Breast Cancer Odds Ratios Associated With Wolfe's Classification of Mammographic Patterns by Percent of Breast Area Containing Mammographic Densities, Breast Cancer Detection and Demonstration Project*

Wolfe pattern (% density)	No. of cases	No. of controls	Odds ratio†	95% confidence interval
N1 (0)	24	48	1.0	Referent
P1 (.1–24.9)	64	88	1.4	(0.8–2.6)
P2	129	111	2.8	(1.6–5.1)
(25–44.9)	45	39	2.4	(1.2–4.8)
(45–64.9)	52	46	3.0	(1.5–5.9)
(≥65)	32	24	3.5	(1.6–7.8)
DY	34	36	2.6	(1.3–5.4)
(<45)	8	17	1.1	(0.4–3.1)
(≥45)	26	18	4.7	(2.0–11.4)

* Unknowns excluded from analysis.

† Adjusted for age at entry (continuous variable), weight at entry (<55, 55–59, 60–64, 65–74, 75+ kg), and number of live births (0, 1, 2, 3, 4+).

Discussion

Our findings suggest that the risk of having breast cancer is positively related to the percentage of mammographic densities observed on screening mammograms taken 4 years before diagnosis. The odds of breast cancer increased steadily with increasing percentage of densities. Women with densities of 65% or greater had a four-fold increase in the odds of breast cancer compared with women with less than 5% densities. This risk was comparable with or greater than that associated with the established risk factors for this disease. In addition, the relation of percent densities to breast cancer was independent and thus could not be explained by recognized breast cancer risk factors, including family history of breast cancer in a mother, sister, or daughter, or age at first live birth. In addition, measurement of percent densities provided better definition of risk than did parenchymal patterns, as demonstrated in the analysis of densities among women in the P2 and DY categories. For instance, P2 women with 65% or more densities had an odds of breast cancer that was almost 50% greater than that for P2 women with less than 45% densities.

Wolfe and colleagues[1] conducted the only other study that used planimetry to determine the association of mammographic densities with risk of breast cancer. Although these investigators found that mammographic densities of 25% or greater were associated with an increased risk of breast cancer, their study differed from the current investigation on several key methodologic aspects. Most important, the mammograms read for the first study were taken at the time of diagnosis and the radiologist was not blinded to disease status as he was in the current study. For this reason, Wolfe *et al.*[1] analyzed percent densities in the opposite unaffected breast, whereas we measured densities in the ipsilateral breast. In addition, the study population of the first study was much smaller and was composed primarily of women who had symptoms of breast disease. Their referent group included women with mammographic densities of less than 25%, whereas the referent group for the current study was restricted to women with less than 5% densities. Ideally, the referent group should include only women with no measurable mammographic densities (*i.e.*, 0% densities).

Other studies that examined the risk of breast cancer associated with mammographic densities conducted visual assessments of the densities and evaluated nodular and homogeneous densities separately.[10-12] Two studies[11,12] found stronger trends in the risk associated with nodular densities, whereas another found that breast cancer risk was more strongly associated with extent of homogeneous densities.[10] The most recent study[12] was of a Canadian screening population, which reported odds ratios very similar to those from our study. The investigators of that study examined nodular and homogeneous densities separately; however, they found that the percentage of the breast containing total densities (nodular + homogeneous densities) was a better indicator of breast cancer risk than the percentage of either nodular or homogeneous densities alone.[12]

A stratified analysis based on a small number of women indicated that a first-degree family history of breast cancer was not a significant risk factor among women with densities of less than 5%. Thus, women with less than 5% densities appear to be protected from the effect of a family history of breast cancer. In a prior analysis,[13] we found that women with the N1 parenchymal pattern and a first-degree family history of breast cancer had a slightly lower risk of breast cancer than N1 women without such a family history for the disease.

Among control women, the extent of mammographic densities decreased with increasing patient age, body weight, and number of live-born children, whereas tall women were more likely than short women to have high-density breasts. Body weight and patient age showed the strongest associations with percent densities. Brisson *et al.*[12] reported similar associations of age, body weight, and parity with the percentage of mammographic densities. Numerous studies have observed that the extent of mammographic densities decreases with age,[14] a phenomenon thought to be the consequence of fatty involution of the breast, which occurs around the time of menopause. Because mammographic densities tend to recede with increasing age, it could be essential to evaluate mammographic densities on mammograms taken several years before the diagnosis of breast cancer.

Our findings and those of Wolfe *et al.*[1] showed no difference in the odds of breast cancer associated with mammographic density among younger and older women. Two studies, however, found positive associations only among women younger than 50 years of age.[10,11]

Several studies have shown strong and consistent associations of body weight with mammographic parenchymal patterns.[3-17] One study evaluated the cross-sectional association of weight with the concentration and percentage of mammographic densities.[15] Increased body weight was associated with a sharp reduction in both the percentage of the breast showing mammographic densities and their concentration.[15] The authors concluded that higher body weight leads to a true reduction in the absolute number of mammographic densities. Clearly, longitudinal studies are needed to understand more fully the relation between weight and the percentage of mammographic densities in the breast.

The potential for bias to affect our study findings was minimized through a number of methodologic features. All mammograms evaluated for this study were taken 4 years before the diagnosis of breast cancer among case subjects, thereby ensuring that the exposure preceded the disease. In addition, the use of prediagnostic mammograms reduced the potential for bias in the assessments of mammographic densities that can occur when a cancer is discernible. Because the reader was blinded to disease status and other characteristics of the study subjects, any misclassification of mammographic densities was likely to be equal among case and control subjects. Whereas many studies evaluated case subjects' contralateral breast, we analyzed the ipsilateral breast and therefore did not have to assume that both breasts had the same percentage of densities.

The potential for masking bias to affect our study findings should also be considered. Masking bias can occur when tumors are concealed in breasts that have high amounts of radiographic densities[18]; such concealment could lead to delays in diagnosis. Two studies[19,20] found that the effects of masking on estimates of relative risk were greatest among studies whose subjects were not regularly screened by mammography and whose cases were diagnosed at the initial mammographic examination.[14] Thus, the effect of masking is likely to be minor in our case–control study of incident breast cancer in a large screening population.

Findings from our reliability study showed that the assessment of mammographic densities is a repeatable intraobserver method. The agreement between the first and second readings, based on five categories of density, was good (77%). This agreement is particularly good considering that the mammograms were taken between 1973 and 1980, a period when image quality was not as good as it is today. Furthermore, the mammograms came from 25 different centers that used different mammography modalities; 66% of the centers used xeromammography, whereas 34% used film-screen.

In conclusion, we found that the quantification of mammographic densities with planimetry is a promising technique that could enhance our ability to identify women at high risk of having breast cancer. Although some brief training on identifying mammographic densities and using the planimeter is necessary, the measurements can be accomplished in a few minutes by mammographers or skilled technicians. With available technology, it may be possible to automate the quantification of mammographic densities, thereby minimizing variation in the measurements. We recommend that reliability studies be conducted to determine how well other radiologists can reproduce measurements of the percentage of mammographic densities in the breast using planimetry.

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